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“One-Stop Shop”: safety of combining transcatheter aortic valve replacement and left atrial appendage occlusion

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Abstract: **OBJECTIVES:** The aim of this study was to investigate the safety and efficacy of combining transcatheter valve replacement (TAVR) and left atrial appendage occlusion (LAAO) versus TAVR alone. **BACKGROUND:** Patients with severe aortic stenosis and atrial fibrillation undergoing TAVR are at increased risk for stroke and bleeding complications. **METHODS:** A cohort of 52 patients undergoing concomitant TAVR and LAAO were compared with 52 patients undergoing isolated TAVR. A primary safety endpoint at 30 days, a clinical efficacy endpoint from day 30 to last follow-up, and an LAAO efficacy endpoint from the first post-interventional day to the last follow-up were chosen. **RESULTS:** The mean age of the study population was 85 ± 5 years. The mean CHA₂DS₂-VASc score and HAS-BLED score were 3.9 ± 1.1 and 2.6 ± 0.9 , respectively. The mean Society of Thoracic Surgeons score was 7.8 ± 5.5 . The median follow-up duration of the study population was 9.4 months (range 0 to 48 months). The primary safety endpoint occurred in 10 patients in the concomitant group and in 7 patients in the isolated TAVR group (19% vs. 14%; 95% confidence interval: 0.59 to 4.06). The clinical and LAAO efficacy endpoints were achieved in 81 (79%) (75% vs. 82%; 95% confidence interval: 0.49 to 2.92) and 75 (73%) patients (69% vs. 76%; 95% confidence interval: 0.54 to 2.51), respectively. **CONCLUSIONS:** This pilot study shows that concomitant TAVR and LAAO is feasible and seems to be safe among patients with severe aortic stenosis and atrial fibrillation. Larger trials and longer follow-up are needed to confirm the safety and efficacy of such an approach.

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STRUCTURAL

“One-Stop Shop”

Safety of Combining Transcatheter Aortic Valve Replacement and Left Atrial Appendage Occlusion



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ABSTRACT

OBJECTIVES The aim of this study was to investigate the safety and efficacy of combining transcatheter valve replacement (TAVR) and left atrial appendage occlusion (LAAO) versus TAVR alone.

BACKGROUND Patients with severe aortic stenosis and atrial fibrillation undergoing TAVR are at increased risk for stroke and bleeding complications.

METHODS A cohort of 52 patients undergoing concomitant TAVR and LAAO were compared with 52 patients undergoing isolated TAVR. A primary safety endpoint at 30 days, a clinical efficacy endpoint from day 30 to last follow-up, and an LAAO efficacy endpoint from the first post-interventional day to the last follow-up were chosen.

RESULTS The mean age of the study population was 85 ± 5 years. The mean CHA₂DS₂-VASc score and HAS-BLED score were 3.9 ± 1.1 and 2.6 ± 0.9 , respectively. The mean Society of Thoracic Surgeons score was 7.8 ± 5.5 . The median follow-up duration of the study population was 9.4 months (range 0 to 48 months). The primary safety endpoint occurred in 10 patients in the concomitant group and in 7 patients in the isolated TAVR group (19% vs. 14%; 95% confidence interval: 0.59 to 4.06). The clinical and LAAO efficacy endpoints were achieved in 81 (79%) (75% vs. 82%; 95% confidence interval: 0.49 to 2.92) and 75 (73%) patients (69% vs. 76%; 95% confidence interval: 0.54 to 2.51), respectively.

CONCLUSIONS This pilot study shows that concomitant TAVR and LAAO is feasible and seems to be safe among patients with severe aortic stenosis and atrial fibrillation. Larger trials and longer follow-up are needed to confirm the safety and efficacy of such an approach. (J Am Coll Cardiol Interv 2016;9:1487-95) © 2016 by the American College of Cardiology Foundation.

Over the past decade, transcatheter aortic valve replacement (TAVR) has emerged as the preferred treatment modality for patients with severe aortic stenosis at high surgical

risk and is now expanding to lower risk patients (1-3). Atrial fibrillation (AF) occurs in more than 10% of octogenarians and is the most common arrhythmia in the TAVR population. It is associated

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ABBREVIATIONS AND ACRONYMS

ACP = Amplatzer Cardiac Plug

AF = atrial fibrillation

CI = confidence interval

LAA = left atrial appendage

LAAO = left atrial appendage occlusion

OAC = oral anticoagulation

STS = Society of Thoracic Surgeons

TAVR = transcatheter aortic valve replacement

TEE = transesophageal echocardiography

TIA = transient ischemic attack

with substantial morbidity and mortality, particularly due to early and late embolic stroke (4-7), bleeding complications (8), and impaired overall outcomes (7,8).

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To prevent thromboembolic strokes in patients with AF, oral anticoagulation (OAC) is the standard treatment for patients with CHA₂DS₂-VASc scores of ≥ 1 (9). However, OAC carries a substantial risk for major bleeding complications (10). The combination of OAC with antiplatelet agents after TAVR potentiates the risk for major bleeding complications (11). In patients with AF undergoing TAVR, bleeding complications were reported to be as high as 50%, and in those

who experience bleeding complications during the first year, 1-year mortality is doubled (8). Therefore, the increased risk for serious bleeding precludes the use of OAC in a significant proportion (30% to 50%) of eligible patients because of relative or absolute contraindications or physician or patient preference (12).

Balancing the risk for embolic and bleeding events in this high-risk population represents a major clinical challenge. Left atrial appendage occlusion (LAAO) offers nonpharmacological stroke protection, obviating the need for OAC. It may therefore be an attractive treatment for the AF TAVR population (13,14) (Figure 1).

We investigated the safety and short-term efficacy of combined procedures (TAVR and LAAO) versus TAVR alone in a contemporary TAVR population with AF.

METHODS

PATIENTS. This was an observational study of consecutive patients undergoing TAVR at the university hospitals of Zurich (463 patients) and Bern (707 patients) from February 2011 to June 2015. The decision of whether to perform concomitant LAAO was random, on the basis of patients' wishes and operators' and treating cardiologists' preferences. All patients had severe aortic stenosis (mean transaortic systolic pressure gradient of ≥ 40 mm Hg or aortic valve area of <1.0 cm² or <0.6 cm²/m²) and were deemed appropriate candidates for TAVR as assessed by the local heart team. All patients had AF with CHA₂DS₂-VASc scores of ≥ 1 . Patients were dichotomized into a "concomitant group" (TAVR and LAAO during the same procedure) and an "isolated TAVR group" (TAVR alone and medical therapy for stroke prevention). All patients gave written informed consent for the

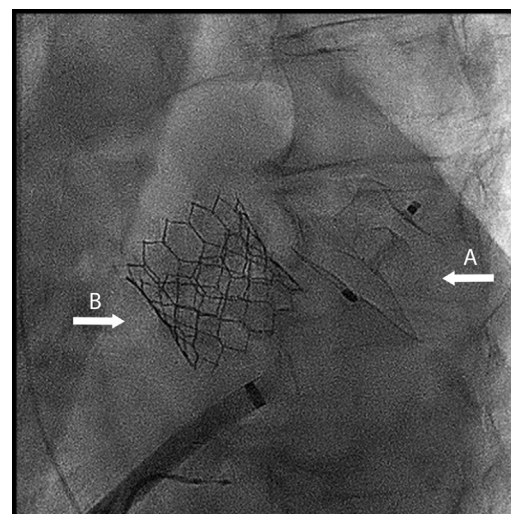
procedure and data collection. Patients were followed within the nationwide Swiss TAVR registry, which was approved by the local ethics committees.

DEVICE. The Amplatzer Cardiac Plug (ACP) (St. Jude Medical, Plymouth, Minnesota) is made of nitinol mesh and filled by polyester to enhance endothelialization and to prevent blood flow through the device. The ACP consists of a lobe with tiny anchoring hooks and a sealing disc. The lobe and disc are connected by a thin, stretchable waist. The ACP is available in lobe sizes from 16 to 30 mm, requiring a 9- to 13-F TorqVue delivery sheath (St. Jude Medical). The second-generation ACP (Amulet) has a recessed screw on the disc to prevent clot formation. Additionally, the lobe comes in larger size ranges (16 to 34 mm) and requires a 12- or 14-F sheath. The larger sizes also feature more anchoring hooks.

PROCEDURE. TAVR was performed using either a transfemoral procedure or, in case of limiting peripheral arterial disease, transapical, subclavian, or direct aortic access. Balloon-expandable as well as self-expandable valve systems were used. Prosthesis size was selected on the basis of annular measurements by multislice computed tomography or transesophageal echocardiography (TEE).

In patients with concomitant interventions, LAAO was performed during the same sitting, usually after TAVR. Pre-procedural imaging of the left atrial appendage (LAA) comprised TEE in all patients. Procedural guidance, for both TAVR and LAAO, was

FIGURE 1 Fluoroscopic Image of a Combined Procedure



(A) Amulet 25-mm left atrial appendage occluder. (B) Edwards SAPIEN 3 26-mm transcatheter heart valve.

based strictly on fluoroscopy, to avoid general anesthesia (except in cases of transapical or transaortic access). The safety of fluoroscopy-guided LAAO has been previously described by our group (15). The left atrium was accessed by transseptal puncture or through a patent foramen ovale or an atrial septal defect (16). Using a Backup Meier wire (Boston Scientific, Natick, Massachusetts), the transseptal sheath was exchanged for the 13-F or 14-F Amplatzer 45°-45°-TorqVue sheath for delivery of the ACP or Amulet. Device sizing relied on contrast injections to the LAA in different angulations. Given the known outer diameter of the delivery sheath (e.g., 5.4 mm for the 14-F sheath), an adequately sized LAA-occluder was chosen, aiming for at least 20% oversizing. After device deployment, a stable device position was confirmed by a tug test and contrast injections. Finally the device was released.

Transthoracic echocardiography was performed before hospital discharge to confirm a stable position of the ACP.

In the concomitant TAVR and LAAO group, OAC was discontinued immediately after LAAO, and patients received dual-antiplatelet therapy with long-term acetylsalicylic acid (100 mg) and clopidogrel (75 mg) for 1 to 6 months. Patients undergoing isolated TAVR were continued on OAC in combination with dual- or single-antiplatelet therapy.

FOLLOW-UP. Patients with combined interventions underwent TEE after 3 to 6 months to confirm a proper sealing of the LAA and to identify residual leaks or thrombi on the device. All patients underwent transthoracic echocardiography at 1 and 12 months after the intervention to confirm proper functioning of the aortic valve prosthesis. Clinical follow-up was performed at the time of TEE and transthoracic echocardiography. In case of an event, hospital charts were reviewed, or the cardiologist or primary care physician was contacted. An independent clinical event committee adjudicated all adverse events according to current criteria.

ENDPOINTS. Three primary endpoints were adapted from Valve Academic Research Consortium 2 (VARC-2) standardized endpoint definitions (17) by including LAAO-specific events.

The primary safety endpoint at 30 days was a composite of all-cause mortality, stroke (disabling and nondisabling) and transient ischemic attack (TIA), bleeding (life threatening), acute kidney injury stage 2 or 3 (according to the Acute Kidney Injury Network system), major vascular complications, clinically significant pericardial effusion requiring pericardiocentesis or resulting in cardiac tamponade, device embolization, and valve failure.

The efficacy endpoints were divided into a “clinical efficacy endpoint” and a “LAAO efficacy endpoint.” The clinical efficacy endpoint included events from day 30 to last follow-up and was defined as freedom from all-cause mortality, all-cause stroke (disabling and nondisabling), and bleeding (life threatening and major) events. The LAAO efficacy endpoint was defined as freedom from all-cause mortality, all-cause stroke (disabling and nondisabling) and TIA, and bleeding (life threatening and major) occurring from the first post-interventional day to the last follow-up.

STATISTICAL ANALYSIS. Data are presented as mean \pm SD or frequencies as appropriate. Baseline patient characteristics between groups (e.g., concomitant TAVR and LAAO vs. isolated TAVR) were compared using unpaired parametric and nonparametric tests as appropriate. For the composite endpoints, time to event after intervention was estimated using the Kaplan-Meier method. Ninety-five percent confidence intervals (CIs) estimated by bivariate Cox regression are presented for the composite and single endpoints between groups. Multivariate Cox regression analysis controlling for age at intervention, sex, and CHA₂DS₂-VASC, HAS-BLED, and Society of Thoracic Surgeons (STS) scores was used to further assess the effect of concomitant LAAO on the composite endpoints. A 2-sided p value ≤ 0.05 was considered to indicate statistical significance for the comparison of the baseline patient characteristics between groups. We did not attempt inferential hypothesis testing for the composite and single endpoint comparisons; thus, 95% CIs rather than p values are presented. Statistical analyses were performed using Stata version 13.1 (StataCorp LP, College Station, Texas).

RESULTS

PATIENT CHARACTERISTICS. The study population comprised 104 patients (59 men, mean age 85 ± 5 years). The mean CHA₂DS₂-VASC score was 3.9 ± 1.1 , the mean HAS-BLED score was 2.6 ± 0.9 , and the mean STS score was 7.8 ± 5.5 . Histories of arterial hypertension were present in 81 patients (78%), diabetes mellitus in 33 (32%), prior ischemic stroke or TIA in 14 (14%), and coronary heart disease in 53 (51%). Five patients (5%) were on dialysis. No significant differences in baseline characteristics were present between the 2 groups (Table 1).

PROCEDURAL INFORMATION. Procedures were performed at the University Hospital Zurich (80 patients [77%]) and at Bern University Hospital (24 patients [23%]) between February 2011 and June 2015. Of the

TABLE 1 Baseline Characteristics

	Overall Population (n = 104)	Concomitant (n = 52)	Isolated TAVR (n = 52)	p Value
Age, yrs	84.6 ± 5.0	84.6 ± 5.7	84.7 ± 4.3	0.969
Male	59 (57)	29 (56)	30 (58)	0.843
CHA ₂ DS ₂ -VASC score	3.9 ± 1.1	4.1 ± 1.2	3.8 ± 0.9	0.232
HAS-BLED score	2.6 ± 0.9	2.7 ± 1.0	2.5 ± 0.9	0.258
STS score	7.8 ± 5.5	8.0 ± 5.3	7.5 ± 5.7	0.301
Hypertension	81 (78)	40 (77)	41 (79)	0.813
Diabetes mellitus	33 (32)	18 (35)	15 (29)	0.527
Paroxysmal atrial fibrillation	45 (43)	24 (46)	21 (40)	0.553
NYHA functional class				0.225
II	28 (27)	12 (23)	16 (31)	
III	56 (54)	33 (64)	23 (44)	
IV	18 (17)	6 (12)	12 (23)	
Prior ischemic stroke or TIA	14 (14)	6 (12)	8 (15)	0.566
CHD	53 (51)	26 (50)	27 (52)	0.844
LVEF, %	53.2 ± 12.4	53.9 ± 11.2	52.6 ± 13.5	0.599
Mean aortic valve gradient, mm Hg	44.3 ± 17.1	44.3 ± 17.6	44.3 ± 16.8	0.997
Aortic valve area, cm ²	0.70 ± 0.2	0.69 ± 0.2	0.72 ± 0.2	0.473
Dialysis	5 (5)	3 (6)	2 (4)	0.647

Values are mean ± SD or n (%).

CHD = coronary heart disease; CHA₂DS₂-VASC = congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke of transient ischemic attack; HAS-BLED = uncontrolled hypertension (>160 mm Hg), renal disease (dialysis, transplantation, creatinine >200 μmol/l), liver disease (cirrhosis or bilirubin >2 times normal or aspartate transaminase, alanine transaminase, or alkaline phosphatase >3 times normal), prior stroke, prior major bleeding or predisposition to bleeding, labile international normalized ratio (time in therapeutic range <60%), age >65 years, medication use predisposing to bleeding (antiplatelet agents, nonsteroidal antirheumatic drugs), alcohol or drug use (≥8 drinks/week); LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack; TAVR = transcatheter aortic valve replacement.

104 patients, 52 underwent TAVR and LAAO in the same procedure (concomitant group), whereas 52 patients underwent TAVR alone (isolated TAVR group). For TAVR, a transfemoral approach was chosen in 92% (85% in the concomitant group, 90% in the isolated TAVR group), transapical access in 6% (12% in the concomitant group, 8% in the isolated TAVR group), direct aortic access in 1% (0% in the concomitant group, 2% in the isolated TAVR group), and left subclavian access in 1% (2% in the concomitant group, 0% in the isolated TAVR group). The CoreValve prosthesis (Medtronic, Minneapolis, Minnesota) was implanted in 50 patients (48%), Edwards SAPIEN XT devices (Edwards Lifesciences, Irvine, California) in 36 patients (34%), Edwards SAPIEN 3 devices in 11 patients (11%), Lotus valves (Boston Scientific, Marlborough, Massachusetts) in 2 patients (2%), and an Acurate TA valve (Symetis SA, Ecublens, Switzerland) in 2 patients (2%), a St. Jude Portico valve (St. Jude Medical) in 1 patient (1%), and a Direct Flow Medical valve (Direct Flow Medical, Santa Rosa, California) in 2 patients (2%). No differences in valve distribution between the concomitant group and the single TAVR group (*p* = 0.439) were observed. Besides TAVR and LAAO, 18 patients (17%) underwent the following additional interventions: 15 patients (29%) in the

concomitant group (percutaneous coronary intervention in 8 patients [15%], iliofemoral stenting in 3 patients [6%], patent foramen ovale or atrial septal defect closure in 3 patients [6%], and MitraClip placement [Abbott Vascular, Santa Clara, California] in 1 patient [2%]) and 3 patients (6%) in the isolated TAVR group (percutaneous coronary intervention in 2 patients [4%] and patent foramen ovale closure in 1 patient [2%]).

PROCEDURAL AND SAFETY OUTCOMES AT 30 DAYS.

The primary safety endpoint occurred in 10 patients in the concomitant group and in 7 patients in the isolated TAVR group (19% vs. 14%; 95% CI: 0.59 to 4.06) (Table 2, Figure 2). Multivariate analysis did not reveal any evidence for a difference between groups (95% CI: 0.59 to 4.29).

There was no procedural neurological complication. Three patients died during the first 30 days after the intervention, 1 in the concomitant group and 2 in the isolated TAVR group. Of those, 2 were cardiovascular (1 in each group) and 1 was a non-cardiovascular death. The noncardiovascular death occurred 3 weeks after TAVR and was due to urosepsis complicated by multiple-organ failure. One cardiovascular death (isolated TAVR group) occurred directly after successful TAVR because of global ischemia with sustained ventricular fibrillation resistant to defibrillation. The other cardiovascular death (concomitant group) happened 2 weeks after the procedure and was due to worsening heart failure. None of the deaths was associated with LAAO. During the first month of follow-up, 1 disabling stroke of ischemic origin (persistent hemiparesis, dysarthria, and dysphagia presumably due to a thromboembolic event arising from a thrombus on the LAAO) occurred in the concomitant group and 3 neurological events in the isolated TAVR group (1 TIA and 2 minor ischemic strokes). In the patient with the disabling ischemic stroke, OAC was restarted and continued.

In both groups, there was 1 life-threatening bleeding complication: 1 bleeding event was due to femoral arteriovenous fistula (concomitant group), and in 1 patient, gastrointestinal bleeding occurred 4 days after the initial intervention because of multiple duodenal ulcers (isolated TAVR group). As expected, the use of contrast dye was higher in the concomitant group compared with the isolated TAVR group (312 ± 148 ml in the concomitant group vs. 98 ± 74 ml in the isolated TAVR group). Five patients had acute kidney injury (2 patients with Acute Kidney Injury Network stage 1 and 3 patients with Acute Kidney Injury Network stage 3), 4 in the concomitant group and 1 in the isolated TAVR group. Three procedural

access-site complications occurred in the concomitant group (1 femoral perforation and 1 arteriovenous fistula with a relevant hematoma, both treated with a Fluency covered stent [Bard Peripheral Vascular, Tempe, Arizona], and 1 dissection of the femoral artery that was treated with uncovered stents).

Cardiac tamponade occurred in 1 patient directly after LAAO and was successfully treated with pericardiocentesis without any long-term sequelae. In 1 patient, transthoracic echocardiography 1 day after the intervention revealed an embolized LAA occluder in the left ventricle. The device was percutaneously snared and removed. The patient then underwent successful implantation of another device.

FOLLOW-UP AND EFFICACY OUTCOMES. The median follow-up duration of the study population was 9.4 months (range 0 to 48 months). The composite clinical efficacy endpoint was achieved in 39 patients in the concomitant group and in 42 patients in the isolated TAVR group (75% vs. 82%; 95% CI: 0.49 to 2.92) (Table 3, Figure 3). The LAAO efficacy endpoint was achieved in 36 patients in the concomitant group and in 39 patients in the isolated TAVR group (69% vs. 76%; 95% CI: 0.54 to 2.51) (Table 3, Figure 4). Multivariate analysis did not reveal a difference between concomitant and isolated interventions for the composite clinical efficacy (95% CI: 0.55 to 3.71) and the LAAO efficacy endpoint (95% CI: 0.52 to 2.63).

At last follow-up, 83 patients (81%) of the total study population were alive. Deaths occurred in 21 patients (20%), of which 18 (86%) were late deaths (>30 days after the initial procedure). Ten patients died in the concomitant group and 8 in the isolated TAVR group (19% vs. 15%). None of the deaths was directly associated with LAAO. Eight deaths were cardiovascular (5 patients in the concomitant and 3 patients in the isolated group) and 10 were noncardiovascular (5 patients in each group). Cardiovascular deaths included 1 patient with coronary triple-vessel disease with sudden cardiac death (concomitant group), 1 patient with progressive heart failure (3 patients in the concomitant and 2 in the isolated TAVR group), and 2 unknown deaths (1 patient in each group). Noncardiovascular deaths occurred because of multiple-organ failure caused by sepsis in 4 patients (2 patients in each group), progressive renal failure in 2 patients (both in the concomitant group), subdural hematoma due to recurrent falls 10 months after the initial procedure in 1 patient (concomitant group), tongue carcinoma in 1 patient (isolated TAVR group), and progressive dementia in 1 patient (isolated TAVR group); 1 patient decided to discontinue dialysis because of his comorbidities (isolated TAVR group).

TABLE 2 Safety Outcome of Combined Interventions Versus Transcatheter Aortic Valve Replacement Alone

	Overall (n = 104)	Concomitant (n = 52)	Isolated TAVR (n = 52)	95% CI
Composite safety endpoint*	17 (16)	10 (19)	7 (14)	0.59–4.06
All-cause mortality	3 (3)	1 (2)	2 (4)	0.46–5.59
Cardiovascular	2 (2)	1 (2)	1 (2)	0.06–15.99
Noncardiovascular	1 (1)	0	1 (2)	0
Stroke and TIA	4 (4)	1 (2)	3 (6)	0.33–3.06
Ischemic stroke	3 (3)	1 (2)	2 (4)	0.044–5.37
Hemorrhagic stroke	0	0	0	0
Life-threatening bleeding	2 (2)	1 (2)	1 (2)	0.06–15.83
Acute kidney injury (stage 2 or 3)	5 (5)	4 (8)	1 (2)	0.45–36.24
Major vascular complication	3 (3)	3 (6)	0	0
Pericardial tamponade	1 (1)	1 (2)	0	0
Device embolization	1 (1)	1 (2)	0	0
Valve failure	0	0	0	0

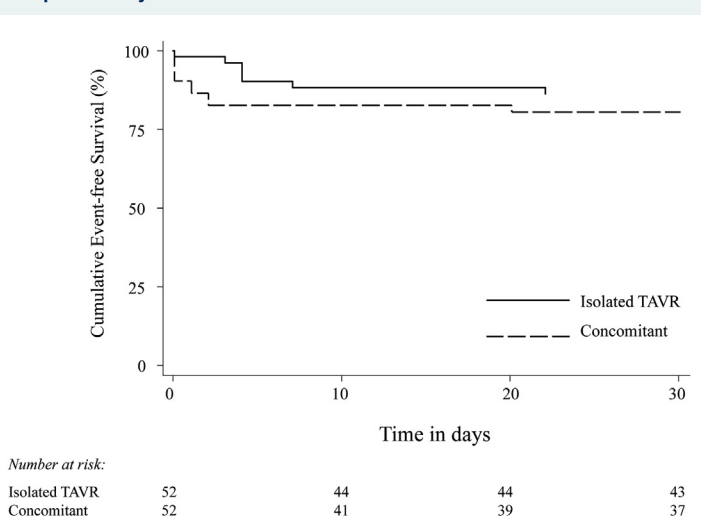
Values are n (%). *Composite of all-cause mortality, all-cause stroke and TIA, bleeding (life threatening), acute kidney injury (stage 2 or 3), major vascular complication, pericardial tamponade, device embolization, and valve failure.

CI = confidence interval; other abbreviations as in Table 1.

Two patients (1 in each group) had late life-threatening bleeding, and 3 patients (concomitant group) had major bleeding complications (all due to gastrointestinal bleeding).

At the time of bleeding, 2 of these patients received acetylsalicylic acid therapy alone, and 1 was receiving dual-antiplatelet therapy (acetylsalicylic acid therapy and clopidogrel). Life-threatening bleeding included the patient with subdural hematoma due to recurrent

FIGURE 2 Kaplan-Meier Survival Curve for Each Group: Freedom From Composite Safety Outcome



95% confidence interval: 0.59 to 4.06. TAVR = transcatheter aortic valve replacement.

TABLE 3 Efficacy Outcome of Combined Interventions Versus Transcatheter Aortic Valve Replacement Alone

	Overall (n = 103)	Concomitant (n = 52)	Isolated TAVR (n = 51)	95% CI
Composite clinical efficacy endpoint*	81 (79)	39 (75)	42 (82)	0.49-2.92
Late all-cause mortality	85 (83)	42 (81)	43 (84)	0.37-2.67
Cardiovascular	95 (92)	47 (90)	48 (94)	0.28-5.78
Noncardiovascular	93 (90)	47 (90)	46 (90)	0.22-3.08
Late all-cause stroke and TIA	103 (100)	52 (100)	51 (100)	
Late bleeding	98 (95)	48 (92)	50 (98)	0.41-34.21
Composite LAAO efficacy endpoint†	75 (73)	36 (69)	39 (76)	0.54-2.51
All-cause mortality	83 (81)	41 (79)	42 (82)	0.39-2.53
Cardiovascular	95 (92)	47 (90)	48 (94)	0.28-5.78
Noncardiovascular	91 (88)	46 (88)	45 (88)	0.26-2.82
Stroke and TIA	99 (96)	51 (98)	48 (94)	0.03-3.06
Ischemic stroke	99 (96)	51 (98)	48 (94)	0.33-3.06
Hemorrhagic stroke	103 (100)	52 (100)	51 (100)	
Post-procedural bleeding	92 (89)	45 (87)	47 (92)	0.53-6.18

Values are n (%). *Freedom from all-cause mortality, all-cause stroke (disabling and nondisabling) and TIA, and bleeding (life threatening and major). †Freedom from all-cause mortality, all-cause stroke (disabling and nondisabling) and TIA, and bleeding (life threatening and major).
LAAO = left atrial appendage occlusion; other abbreviations as in Tables 1 and 2.

falls (concomitant group) and 1 patient with upper gastrointestinal bleeding receiving supratherapeutic OAC with warfarin.

OAC was continued for some additional period after LAAO in 5 of the 52 patients (10%). The reasons varied among patients: thrombus on the device (n = 2), physician order (n = 1), heparin-induced thrombocytopenia (n = 1), and unknown reasons

(n = 1). The 2 patients with a thrombus on the device continued with OAC because of physician order and patient wish. In the patient with heparin-induced thrombocytopenia, OAC with rivaroxaban 20 mg was continued for 6 weeks after the intervention. Eight patients (16%) in the isolated TAVR group received no OAC. Duration and type of antiplatelet therapy varied among patients and depended on physician order. In the isolated TAVR group, 8 patients (16%) at discharge were treated with triple therapy (acetylsalicylic acid, clopidogrel, and OAC); 24 patients (47%) received dual therapy (either acetylsalicylic acid or clopidogrel and OAC), 11 patients (22%) received OAC alone; 7 patients (14%) were treated with acetylsalicylic acid and clopidogrel or ticagrelor, 1 patient was on clopidogrel alone. Of those patients receiving OAC, most were treated with warfarin (86%), and additional antiplatelet therapy was prescribed for 1 to 12 months.

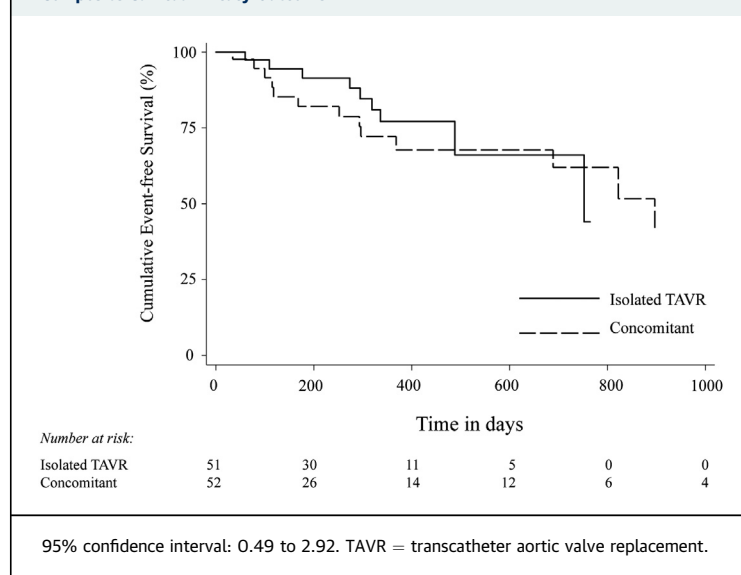
DISCUSSION

The goal of this pilot study in patients with severe aortic stenosis was to investigate the outcomes of combined procedures (TAVR and LAAO) and TAVR alone. The main findings were that: 1) combining TAVR with LAAO was safe and did not result in adverse procedural outcome; 2) there was no difference in efficacy after a mean follow-up period of 9.4 months; 3) these findings held true after multivariate analysis adjusted for age, sex, and CHA₂DS₂-VASC, HAS-BLED, and STS scores; and 4) most (88%) safety events occurred in the first 7 days after the intervention.

PROCEDURAL AND CLINICAL SAFETY OUTCOMES.

As previously shown, LAAO has the potential to prevent ischemic stroke as well as bleeding complications in patients with AF (13,14,18). Because patients in AF undergoing TAVR are at high risk for bleeding and thromboembolic events, combining TAVR and LAAO appears to be a reasonable approach to prevent these complications. However, LAAO is a technically demanding procedure with a flat learning curve (15,16). Therefore, complication rates of LAAO are clinically significant and strongly related to operator experience (19,20). Because of the additional venous access, the transseptal puncture, the increased procedural time, and the extra contrast dye required, LAAO after TAVR potentially bears an increased risk for adverse procedural events. However, our results suggest that the procedure can be performed safely in addition to TAVR in experienced hands.

FIGURE 3 Kaplan-Meier Survival Curve for Each Group: Freedom From Composite Clinical Efficacy Outcome



In line with recently published data, most safety events (88%) in the present study were a result of periprocedural complications or occurred early after the intervention (<7 days) (13,21). Safety events strictly related to LAAO, such as cardiac tamponade and embolization of the LAA closure device, occurred in only 2 patients (5%). Device embolization was previously reported in 0.8% to 3.9% and was limited mainly to the early post-procedural period (18,22). Cardiac tamponade in our patient cohort was low (2%), in line with published data (1.2% to 5%) (13,18,19), and neither device embolization (23) nor tamponade resulted in any long-term sequelae.

Although periprocedural complications are thought to be higher in patients undergoing concomitant TAVR and LAAO, we did not observe higher 30-day event rates of clinically significant bleeding (2%), access-site complications (6%), and acute kidney injury stage 2 or 3 (8%) compared with studies of patients undergoing TAVR alone. Thirty-day outcomes in recent trials with patients undergoing TAVR showed event rates of major vascular complications of 5.3% to 6.5%, clinically significant bleeding of 4.0% to 13.6%, and acute kidney injury of 2.7% to 18.7% (3,24,25). A word of caution is needed for patients with reduced kidney function, because concomitant procedures required a higher procedural amount of contrast dye. However, patients with kidney failure are exposed to a higher bleeding risk and may particularly benefit from concomitant LAAO. Of note, in the concomitant patient population, additional procedures (besides LAAO) were performed much more frequently than in the isolated TAVR group (29% vs. 6%).

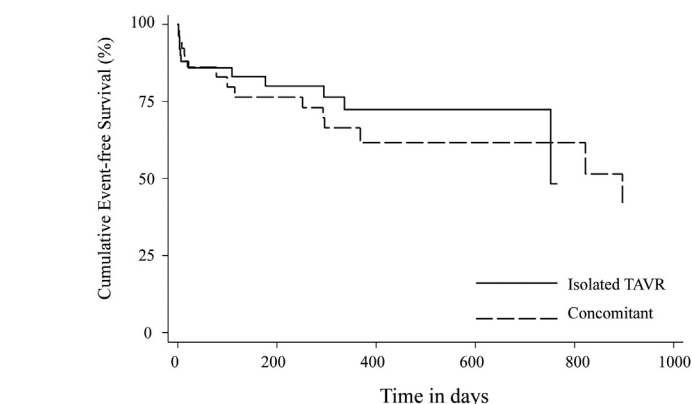
In summary, concomitant LAAO in patients undergoing TAVR does not seem to affect the success rate or outcome of TAVR.

CLINICAL AND LAAO EFFICACY OUTCOMES.

After 3.8 years of follow-up, the superiority of LAAO compared with OAC with warfarin was shown in a randomized trial (14), which was in line with a large multicenter registry with the ACP (18) with a follow-up period of 13 months. The potential advantage of LAAO over vitamin K antagonists (i.e., reduction of bleeding and ischemic stroke) became more prominent with longer follow-up (15,26).

In our study, we could not show any difference in efficacy outcomes between the 2 groups, presumably due to a too short follow-up period and small patient number (9.4 months vs. 3.8 years and 13 months, respectively, in the previously mentioned studies including larger numbers of patients). However, it is likely that the advantage of LAAO becomes evident

FIGURE 4 Kaplan-Meier Survival Curve for Each Group: Freedom From Composite Left Atrial Appendage Occlusion Efficacy Outcome



95% confidence interval: 0.54 to 2.51. TAVR = transcatheter aortic valve replacement.

only after longer follow-up. Furthermore, ischemic strokes were a relatively rare event in our study population, thereby further limiting statistical power.

The second composite LAAO efficacy endpoint was chosen to assess early efficacy, excluding procedural events, which account for the largest share according to the PROTECT-AF (Watchman Left Atrial Appendage Closure Device for Embolic Protection in Patients With Atrial Fibrillation) trial. Although warfarin was stopped directly after LAAO in most patients, no difference in the composite of mortality, neurological events, and bleeding complications was noted. As mentioned previously, this finding supports the evidence that the benefit of LAAO over vitamin K antagonists materializes, if at all, only after a longer follow-up period.

Another interesting finding is the diversity of antithrombotic regimens in the isolated TAVR group. Given the high-risk population, treating physicians seem reluctant to put TAVR patients on OAC. This in return puts those patients at very high risk for stroke complications (27), indicating the dilemma we are facing in these patients.

LAAO seems to be a valuable alternative for OAC, especially in these high-risk patients. The question remains, however, if concomitant procedures are preferable to a staged approach, as described in a case report by Bogunovic et al. (28). In our opinion, concomitant procedures are not only feasible in experienced hands but also have several advantages: patients undergoing TAVR and LAAO in the same

sitting are immediately protected from stroke and bleeding complications, and a single-session approach seems patient-friendly for older and multimorbid patients (29).

STUDY LIMITATIONS. The main goal of this pilot study was an initial proof of concept to demonstrate the safety of combining TAVR with LAAO. Conclusions on safety and efficacy are only hypothesis generating, because the main limitation of the study arises from the relatively small number of patients and the short follow-up period, which limits the power of the analysis. Certain design limitations are inherent, including the retrospective nature of this study and the possible selection bias due to the lack of selecting a propensity-matched cohort. However, comparison of the isolated TAVR group with the remaining patients with AF in the TAVR cohort of the University Hospital Zurich shows no remarkable difference in risk factors (STS score, sex, diabetes, hypertension, stroke, and coronary artery disease).

LAAO is considered an intricate procedure, with a flat learning curve. Therefore, our results may represent the outcomes of high-volume centers with many years of experience with LAAO and may therefore not be generalizable.

Furthermore, the diversity of therapeutic regimens for OAC might have influenced outcomes of the presented study population. Therefore, a larger, randomized study is needed to show safety and efficacy of combined interventions. For a future study, the total estimated sample size for the composite safety endpoint on the basis of 80% power to confirm noninferiority (1-sided confidence level of 97.5%)

would be 484 (assuming an event rate of 19% and considering that a difference in the composite safety event rate as large as 10% in favor of the single TAVR procedure would allow the concomitant TAVR procedure to be noninferior).

CONCLUSIONS

Combining TAVR with LAAO is feasible and seems to be safe. A larger randomized trial with longer follow-up is needed to confirm safety and to further show the efficacy of combining these 2 interventions.

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PERSPECTIVES

WHAT IS KNOWN? Patients with severe aortic stenosis and AF undergoing TAVR are at increased risk for stroke and bleeding complications.

WHAT IS NEW? LAAO offers nonpharmacological stroke protection, obviating the need for OAC. Combining TAVR and LAAO in the same sitting is feasible and seems to be safe.

WHAT IS NEXT? To show the safety and efficacy of combining TAVR and LAAO in these patients, a larger randomized trial with longer follow-up is needed.

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